

Assessment of Therapeutic Equivalence of Three Proportions Using a Bayesian Approach

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Abstract: Nonrejection of the null hypothesis when comparing two response rates in a clinical trial does not necessarily imply that the two treatments are equivalent with respect to their therapeutic effectiveness. Recently, researchers have invested much time and effort in describing situations in which therapeutic equivalence (TE) may be achieved. These have involved direct hypothesis testing procedures and confidence interval techniques. The latter involves determining if such an interval lies within predefined equivalent regions. The focus is to determine if three treatments are equivalent with respect to their therapeutic effectiveness. The prior involves the natural conjugate beta family of distributions. The primary parameter of interest is the ratio of the two binomial parameters. Limiting values of the hyperparameters of the conjugate family are used to demonstrate the robustness of the outcomes. Several equivalence regions are utilized to test whether or not equivalence has been achieved and under what conditions the attainment of equivalence may not be established. For foundation purposes, two proportions are discussed. An extension is given to three proportions. An illustrative example is provided.

Keywords: Beta-Binomial; therapeutic equivalence; Monte Carlo method; clinical trials

1. INTRODUCTION

Most phase III studies are designed with several endpoints in mind. One of these endpoints is the rate or proportion. In a clinical trial, interest sometimes focuses on the question of which therapy produces the highest proportion of successes or responses. Response can be defined according to the criteria given in a treatment protocol. Proportions are used to depict the percentage of patients in a given trial or on a particular treatment who have certain characteristics.

Although there are numerous techniques based on classical statistical approaches, it is worth mentioning that the Bayesian approach has come to the forefront in the literature.

Appropriate statistical methodologies have been developed for deriving the expression for the posterior distribution of the difference of two proportions [Pham-Gia and Turkkan, 1993].

2. THE POSTERIOR DENSITY FOR TWO PROPORTIONS

Methodology and notation are developed in order to fulfill the research objectives. The development begins with the comparison of two proportions, p_1 and p_2 . We are interested in testing

$$H_0: \eta \leq 1 - \theta \quad (1)$$

versus the alternative

$$H_a: 1 - \theta < \eta < 1 + \theta \quad (2)$$

where, $\eta = p_1 / p_2$ and $\theta = 0.2$.

First, let p_i represent the proportions, where

$i = 1, 2$. The prior density is given by

$$\pi(p_i) = \frac{1}{\beta(\alpha, \beta)} (p_i)^{\alpha-1} (1-p_i)^{\beta-1} \quad (3)$$

where, $\alpha > 0$, $\beta > 0$, and $0 \leq p_i \leq 1$.

Furthermore, the likelihood function is given by

$$l(p_i) = p_i^{y_i} (1-p_i)^{n_i-y_i} \quad (4)$$

where, $i = 1, 2$ and y_i is the number of successes in n_i trials.

To derive the density of the ratio of proportion 1 and proportion 2, we first obtain the joint prior density and joint likelihood functions. Assuming independence, the joint prior is as follows:

$$\pi(p) = \frac{1}{\beta(\alpha, \beta)} (p_1)^{\alpha-1} (1-p_1)^{\beta-1} \frac{1}{\beta(\alpha, \beta)} (p_2)^{\alpha-1} (1-p_2)^{\beta-1} \quad (5)$$

$$= \left(\frac{1}{\beta(\alpha, \beta)} \right)^2 (p_1)^{\alpha-1} (1-p_1)^{\beta-1} (p_2)^{\alpha-1} (1-p_2)^{\beta-1}$$

In addition, the joint likelihood

$$\Pi(p) = p_1^{y_1} (1-p_1)^{n_1-y_1} p_2^{y_2} (1-p_2)^{n_2-y_2} \quad (6)$$

The transformation is as follows. Let

$$\eta_1 = \frac{p_1}{p_2} \quad \xi = p_2$$

then $\eta_1 \xi = p_1$. The absolute value of the Jacobian is

$$|J| = \begin{vmatrix} \frac{\partial p_1}{\partial \xi} & \frac{\partial p_1}{\partial \eta_1} \\ \frac{\partial p_2}{\partial \xi} & \frac{\partial p_2}{\partial \eta_1} \end{vmatrix} = \begin{vmatrix} \eta_1 & \xi \\ 1 & 0 \end{vmatrix} = |-\xi| = \xi$$

Now, rewriting p_1 and p_2 , we have

$$g(\xi, \eta_1) = \left(\frac{1}{\beta(\alpha, \beta)} \right)^2 (\eta_1 \xi)^{\alpha-1} (1-\eta_1 \xi)^{\beta-1} (\xi)^{\alpha-1} (1-\xi)^{\beta-1} \xi$$

and

$$l(\xi, \eta_1) = (\eta_1 \xi)^{y_1} (1-\eta_1 \xi)^{n_1-y_1} (\xi)^{y_2} (1-\xi)^{n_2-y_2}$$

So, the posterior density is

$$p(\eta_1 | data) = \frac{\int_0^1 \left(\frac{1}{\beta(\alpha, \beta)} \right)^2 (\eta_1 \xi)^{y_1+n_1-1} (1-\eta_1 \xi)^{n_1-y_1-1} (\xi)^{y_2+n_2-1} (1-\xi)^{n_2-y_2-1} d\xi}{\int_0^1 \int_0^1 \left(\frac{1}{\beta(\alpha, \beta)} \right)^2 (\eta_1 \xi)^{y_1+n_1-1} (1-\eta_1 \xi)^{n_1-y_1-1} (\xi)^{y_2+n_2-1} (1-\xi)^{n_2-y_2-1} d\xi d\eta_1}$$

Hence, the posterior density of the ratio of two proportions is given by

$$p(\eta | data) = \frac{\int g(\xi, \eta_1) l(\xi, \eta_1) d\xi}{\iint g(\xi, \eta_1) l(\xi, \eta_1) d\xi d\eta_1} \quad (7)$$

where, $g(\xi, \eta_1)$ denotes the joint prior density function, $l(\xi, \eta_1)$ denotes the joint likelihood function, $\eta_1 = p_1/p_2$, and $\xi = p_2$.

3. THE CONFIDENCE REGION FOR TWO PROPORTIONS

A basic problem when assessing equivalence is specification of an acceptable difference. The FDA Guidelines specified 20 percent for comparative bioavailability studies. In other circumstances, such a specified limit may not be as clear-cut. If we let $p(\Delta)$ represent the p-value associated with an equivalence test using limits $\pm \Delta$ [or $p(C)$ for limits $\pm C$], we can then examine a plot of $p(\Delta)$ against Δ or $p(C)$ against C . The results of the confidence regions in Table 1 are for various values of α and β . These calculations were done using MathCad® 8. MathCad® is a standard calculation software by MathSoft®, Inc.

The ratio within Table 2 was evaluated using several combinations of α and β . For justification of these values, see Birch and Bartolucci [1983]. For the purpose of discussion, a few combinations of α and β are as follows:

Table 1. Confidence Regions for Ratio of Two Proportions ($\alpha = .1$)

Prior Parameters			
α	β	Lower endpoint	Upper endpoint
2	3	1.048	1.972
3	2	1.019	1.941
2	2	1.045	1.969

For these calculations, p_1 is the proportion of CHOP (cytoxan, adriamycin, vincristine, and prednisone) and p_2 is the proportion of BCOP (BCNU, cytoxan, vincristine, and prednisone), where CHOP and BCOP are two treatments being compared in diffuse histiocytic non-Hodgkin's lymphoma in a Cooperative Cancer Study Group protocol.

At the given ($\alpha=.1$) level, we observe that both of the confidence endpoints are not within the equivalence region of (.441, 1.558), which was calculated using the formula $(1-.2/p_2, 1+.2/p_2)$, derived from the relationship, $p_1 - p_2 < 0.20$ [Hauck and Anderson, 1986], where $p_2 = 19/53$. All information needed to obtain the endpoints of the equivalence regions are derived from the density given by equation (8).

Table 2. Bayes' Estimates.

α	β	$\frac{\hat{p}_1}{\hat{p}_2}$
2	3	1.51
3	2	1.48
2	4	1.51
2	2	1.51

4. THE POSTERIOR DENSITY FOR THREE PROPORTIONS AND THE INTEGRATION METHOD

Applications having multiplicities are among the most difficulties faced by researchers. Unfortunately, this happens frequently in Bayesian analysis. Multiple comparisons often invoke

analytically intractable solutions. Oftentimes, integrands do not behave well in certain regions.

One must pursue numerical methods of integration when the multiple integration is nontractable.

The analyst uses the numerical methods of multiple integration to change the integrand such that it is computable within the range of interest.

Even though there are several problems that may occur when computing multiplicities, one must remember that the overall most important task of the Bayesian analyst is to complete the statistical inference process. Determining the posterior density for the three proportions presents many challenges. The formula for the posterior is as follows:

$$p(\eta_1, \eta_2 | data) = \frac{\int g(\xi, \eta_1, \eta_2) l(\xi, \eta_1, \eta_2) d\xi}{\int \int \int g(\xi, \eta_1, \eta_2) l(\xi, \eta_1, \eta_2) d\xi d\eta_1 d\eta_2} \tag{8}$$

where,

$$\eta_1 = \frac{p_1}{p_2} \quad \eta_2 = \frac{p_1}{p_3} \quad \xi = p_1$$

The numerator was calculated directly. On the other hand, the denominator had to be integrated using a change of variables. Let

$$\eta_1 = \frac{p_1}{p_2} \quad \eta_2 = \frac{p_1}{p_3} \quad \xi = p_1$$

then

$$p_2 = \frac{\xi}{\eta_1} \quad p_3 = \frac{\xi}{\eta_2}$$

The absolute value of the Jacobian is

$$|J| = \begin{vmatrix} \frac{\partial \eta_1}{\partial \xi} & \frac{\partial \eta_1}{\partial \eta} \\ \frac{\partial \eta_2}{\partial \xi} & \frac{\partial \eta_2}{\partial \eta} \end{vmatrix} = \begin{vmatrix} \eta_1 & \xi \\ 1 & 0 \end{vmatrix} = |-\xi| = \xi$$

The prior is $\pi(p_i) = \frac{1}{B(\alpha, \beta)} p_i^{\alpha-1} (1-p_i)^{\beta-1}$ and

the likelihood function is

$$l(p_i) = p_i^{y_i} (1-p_i)^{n_i-y_i}$$

where $i=1,2,3$ and y_i is the number of successes in n_i trials for the i th proportion.

The joint prior is as follows:

$$g(\xi, \eta_1, \eta_2) = \left(\frac{1}{B(\alpha, \beta)} \right) (\xi)^{\alpha-1} (1-\xi)^{\beta-1} \left(\frac{\xi}{\eta_1} \right)^{\alpha-1} \left(1 - \frac{\xi}{\eta_1} \right)^{\beta-1} \left(\frac{\xi}{\eta_2} \right)^{\alpha-1} \left(1 - \frac{\xi}{\eta_2} \right)^{\beta-1} \frac{\xi^2}{\eta_1^2 \eta_2^2}$$

The joint likelihood function is as follows:

$$l(\xi, \eta_1, \eta_2) = (\xi)^{y_1} (1-\xi)^{n_1-y_1} \left(\frac{\xi}{\eta_1} \right)^{y_2} \left(1 - \frac{\xi}{\eta_1} \right)^{n_2-y_2} \left(\frac{\xi}{\eta_2} \right)^{y_3} \left(1 - \frac{\xi}{\eta_2} \right)^{n_3-y_3}$$

A separate procedure was done to obtain $\eta_3 = p_3/p_2$. This procedure yielded $P(\eta_3|data)$. To find the density of $\eta_3 = p_3/p_2$, we let

$$T = \frac{\eta_1}{\eta_2}$$

where, T is η_3 . Thus,

$$T = \frac{\eta_1}{\eta_2} \qquad X = \eta_2$$

then $\eta_1 = TX$

The absolute value of the Jacobian is:

$$|J| = \begin{vmatrix} x & 0 \\ 1 & 1 \end{vmatrix} = X$$

Assuming η_1 and η_2 are independent, the following expression is obtained:

$$f(\eta_1, \eta_2) = \int p(\eta_1, \eta_2 | data) d\eta_1 \int p(\eta_1, \eta_2 | data) d\eta_2$$

and substitution is used for deriving the expression for $f(T, X)$. Hence,

$$f(T) = \int f(T, X) dx.$$

5. NUMERICAL EXAMPLE FOR TWO PROPORTIONS

Hayward et al. [1977] give well-defined response criteria for metastatic breast cancer. CHOP (cytoxan, adriamycin, vincristine, and prednisone) was compared to BCOP (BCNU, cytoxan, vincristine, and prednisone) in diffuse histiocytic non-Hodgkin's lymphoma in a Cancer Study Group protocol.

There were 53 patients randomized and evaluated on BCOP and 59 patients randomized and evaluated on CHOP. The complete responses were considered. There were 19 complete responses (CR) on BCOP and 33 CR on CHOP. Using Bayes' estimates we can get the confidence regions for the ratio of two proportions. The prior parameters are $\alpha = 2$ and $\beta = 3$. Using these prior parameters, a confidence region of (1.048, 1.972) is obtained by plugging in the actual data into the derived confidence region formula. Related work in this area has been done by Birch and Bartolucci [1983], Bartolucci and Singh [1993] and Singh [1996]. It is obvious that at the ($\alpha = .1$) level, we can see that both of the confidence endpoints are not within the equivalence region of (.441, 1.558). Based on the specified width, 0.20, of the region from the Food and Drug Administration, it is concluded that a necessary condition for equivalence has not been obtained.

6. NUMERICAL EXAMPLE FOR THREE PROPORTIONS

Patients were randomized to one of three treatments in an advanced non-small-cell carcinoma of the lung trial. Patients were appropriately stratified. The treatments were as follows: (a) CAMF (cyclophosphamide, adriamycin, methotrexate with folinic acid), (b) CAP (cyclophosphamide, adriamycin, cis-platinum), and (c) CA (cyclophosphamide, adriamycin). The total number of observations involved in the analyses was 339. The three treatments were to be compared with respect to their ability to achieve a CR or partial response (PR). There were 13 responses out of 98 possibilities for treatment CAMF. The treatment CAP had a response proportion of 9 out of 113. There were 4 responses out of 128 for CA.

The third data set, a test set, consists of three treatments. The three treatments were PA, which had a response of 13 out of 20; CT with 12 out of 20 responses; and ON, which had 11 out of 20 responses.

It is possible to do a pairwise comparison of three proportions using Bayes' estimates. Confidence

regions for the posterior of the ratio of proportions is obtainable. The confidence regions for the prior parameters $\alpha = 2$ and $\beta = 3$ are p_1 / p_2 (1.445,1.675), p_1 / p_3 (1.565,2.027) and p_3 / p_2 (0.751,0.989). Using the sample data, the pairwise comparison of three proportions at $\alpha = .1$ yields the following confidence regions for the posterior of the ratio of proportions:

p_1 / p_2 (0.899,1.260)
 p_1 / p_3 (1.002,1.358)
 p_3 / p_2 (0.703,1.137)

Hence p_1 / p_2 and p_3 / p_2 fall within (0.667,1.333) and p_1 / p_3 , falls within (0.636,1.364). The intervals (0.667, 1.333) and (0.636, 1.364) were calculated using the formula for the equivalence region endpoints, $(1-.2/p_2, 1+.2/p_2)$, [Hauck and Anderson, 1986] where, p_2 is 12 / 20 and $(1-.2/p_3, 1+.2/p_3)$ where, p_3 is 11 / 20, respectively. The p 's are estimated. The endpoints of the confidence regions from the cancer data does not fall within the equivalence region, but the endpoints from the sample data do.

7. CONCLUSIONS

In this paper, we considered the problem of assessing therapeutic equivalence of three independent proportions. Main areas of this research relate to equivalence, the integration involved in determining the posterior densities, inference constructions, and the basis for establishing a sufficient condition for equivalence.

This research assumed that all p_i 's were independent. It would be of great interest to continue this research with the assumption that the p_i 's are not independent. One possible method to be explored for this dependence assumption is the concept expressed in the De Finetti theorem on exchangeable variables. This theorem is as follows: To every infinite sequence of exchangeable random variables (X_n) having values in $\{0,1\}$, there corresponds a probability distribution F concentrated on $[0, 1]$ such that:

$$P\{X_1 = 1, \dots, X_k = 1, X_{k+1} = 0, \dots, X_n = 0\}$$

$$= \int_0^1 \Theta^k (1-\Theta)^{n-k} F(d\Theta) \text{ for all } n \text{ and } 0 \leq k \leq n.$$

The distribution F may be regarded as the prior for the random parameter Θ [Heath & Sudderth, 1976]. Exchangeable is defined as follows: The random variables, X_1, \dots, X_n are exchangeable if the $n!$ permutations, have the same n -dimensional probability distribution [Freedman & Diaconis, 1980]. This paper presented some issues pertaining to the integration involved in deriving the posterior density for the

$$(X_{k_1}, \dots, X_{k_n})$$

pairwise comparison of three proportions. There is definitely a need for the development of more methods that would be beneficial in handling multi-dimensional integration problems from a computational perspective.

Moreover, the triple integral in this research involved some beta functions with very interesting behavior. It would be of interest to direct attention to the study of the behavior of such complicated functions.

Calculations from this research were done using the Monte Carlo method as well as basic integration principles. But other methods, such as the Gibbs sampling algorithm, need more exploration.

This research may appear to be directed toward the Bayesian statistician; however, other areas of statistics and mathematics would benefit greatly from further research in this area. For example, even though the subject of power is inconsistent in our Bayesian framework, it would be of interest to see how it would be applicable in this research. Hauck and Anderson [1992] presented types of bioequivalence and some related considerations. Their work has two main areas where further research is needed. First, statisticians need methods for assessing population bioequivalence and methods for individual bioequivalence. Second, there is a need for more methods that are appropriate for measures of bioavailability.

The encouragement of the development of other statistical inference constructions should be included because of the diversity of trials regarding the manner in which data is collected and because the amount of information available before, during, and after the trial needs to be handled. In addition, other statistical inference constructions to the problem of equivalence bring new ideas that complement previous ones and help others unfold.

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